ACUTE TOXICITY SUMMARY

FORMALDEHYDE

(methanal, oxomethane, oxymethylene, methylene oxide, formic aldehyde, methyl aldehyde)

CAS Registry Number: 50-00-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**94 μg/m³**
Critical effect(s)	eye irritation
Hazard Index target(s)	Eyes; Respiratory System; Immune System

II. Physical and Chemical Properties (HSDB, 1993)

Description	colorless gas
Molecular formula	CH_2O
Molecular weight	30.03
Density	0.815 g/L @ -20°C
Boiling point	-19.5°C
Melting point	-92°C
Vapor pressure	3883 mm Hg @ 25°C (Howard, 1989)
Flashpoint	300° C or 573°F
Explosive limits	upper = 73% lower = 7%
Solubility	soluble in water, alcohol, ether, other polar solvents
Odor threshold	0.05-0.5 ppm
Odor description	very pungent odor; straw-like
Metabolites	formic acid
Conversion factor	1 ppm = 1.24 mg/m³ @ 25°C

III. Major Uses or Sources

Formaldehyde is used in the manufacture of melamine, polyacetal, and phenolic resins. It is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids. Mobile home interiors and pressed wood furniture are two other common sources of formaldehyde exposure.

IV. Acute Toxicity to Humans

Exposure to moderate levels of formaldehyde (1-3 ppm) can result in eye and upper respiratory tract irritation (Weber-Tschoppe *et al*., 1977; Kulle *et al*., 1987). Feinman (1988) states that most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs. High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984).

A few human case studies report severe pulmonary symptoms. A medical intern with known atopy and exposure to formaldehyde over a period of 1 week developed dyspnea, chest tightness, and edema, following a final 2 hour exposure to high concentrations of formaldehyde (Porter, 1975). Five workers exposed to high concentrations of formaldehyde from urea-formaldehyde foam insulation experienced intolerable eye and upper respiratory tract irritation, choking, marked dyspnea, and nasal obstruction (Solomons and Cochrane, 1984). However, the concentration of formaldehyde and the contribution of other airborne chemicals were unknown in both of the reports.

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects (Harving *et al*., 1990; Kulle *et al*., 1987; Sheppard *et al*., 1984; Witek *et al*., 1986; Witek *et al*., 1987; Schachter *et al*., 1986; Schachter *et al*., 1987; Sauder *et al*., 1986; Sauder *et al*., 1987; Frigas *et al*., 1984; Uba *et al*., 1989; Akbar-Khanzadeh *et al*., 1994). Short exercise sessions during exposure on a bicycle ergometer were included in some of the studies. Concentrations of formaldehyde in the human exposure studies ranged as high as 3 ppm for up to 3 hours. The major findings in these studies were mild to moderate eye and upper respiratory tract irritation, typical of mild discomfort from formaldehyde exposure.

In a human irritation study by Weber-Tschoppe *et al*. (1977), 33 subjects were exposed to formaldehyde at concentrations ranging from 0.03-3.2 ppm (0.04-4.0 mg/m^3) for 35 minutes. Thresholds were 1.2 ppm (1.5 mg/m^3) for eye and nose irritation, 1.7 ppm (2.1 mg/m^3) for eye blinking, and 2.1 ppm (2.6 mg/m^3) for throat irritation.

Kulle *et al*. (1987) exposed nonasthmatic humans to up to 3.0 ppm (3.7 mg/m^3) formaldehyde in a controlled environmental chamber for 3 hours. Significant dose-response relationships were seen with odor and eye irritation. At 0.5 ppm for 3 hours, none of 9 subjects had eye irritation. At 1.0 ppm, 3 of 19 subjects reported mild eye irritation and one experienced moderate irritation. At 2.0 ppm, 6 subjects reported mild and 4 reported moderate eye irritation. Nasal flow resistance was increased at 3.0 ppm but not at 2.0 ppm (2.5 mg/m^3). There were no significant decrements in pulmonary function nor increases in methacholine induced bronchial reactivity as a result of 3-hour exposures to 0.5-3.0 ppm (0.6-3.7 mg/m^3) formaldehyde at rest or at exercise, including 24 hours post exposure.

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m^3 formaldehyde for 2 hours (Pazdrak *et al*., 1993). Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure. Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in

nasal lavage fluid 4 and 18 hours after exposure. No differences were found between patients with skin sensitization and healthy subjects.

In a study by Green *et al*. (1987), volunteer asthmatic and normal subjects exposed to formaldehyde developed clinically significant decrements in pulmonary function. Exposure to 3 ppm formaldehyde for 1 hour resulted in clinically significant reductions of FEV_1 (defined as > 20% or more) and FEV_1/FVC (ratio 70% or less) in 5 individuals in the study (2 of 16 asthmatics, 2 of 22 normal subjects, and one clinically normal subject with hyperactive airways). Of these individuals, 3 had reductions of FEV_1 of 20% or more during exposure. One of 22 asthmatics had a greater than 20% reduction in FEV_1 (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation [V_E] = 30-40 l/min), which, according to the authors, was low enough to prevent exercise-induced bronchospasm. One of 22 normal subjects also exhibited a greater than 20% clinically significant reduction in FEV_1 (-24.4%) and in FEV_1/FVC, which occurred at 47 minutes into exposure to 3 ppm formaldehyde. These reductions occurred following a second 15 minute heavy exercise session (V_E = 60-70 l/min) near the end of the 1 hour exposure period. A third asymptomatic "normal" subject with hyperactive airways had a clinically significant reduction of FEV_1 (-20.5%) at 17 minutes, following the first heavy exercise session. This subject exhibited occult airway hyperactivity and was excluded from analysis with the other exposure groups due to his respiratory condition. Subjects exhibiting reductions in FEV_1 of greater than 20% following exposure also exhibited FEV_1/FVC ratios of less than 70%. However, none of the subjects in the study exhibited a clinically significant reduction of 50% or greater in airway conductance (SG_{aw}) during exposure to 3 ppm formaldehyde. Other than mild nose and throat irritation, no severe respiratory signs and symptoms were apparently reported.

Sim and Pattle (1957) exposed twelve men to 17.3 mg/m³ (13.9 ppm) formaldehyde for 30 minutes. This concentration caused "considerable nasal and eye irritation when they first entered the chamber; but despite the continued mild lacrimation for some period of time, there was no marked response (pulmonary or cardiovascular) to the exposure." The eye irritation was not severe, according to the authors, and resolved after 10 minutes in the chamber.

Kriebel and associates (1993) studied 24 physical therapy students dissecting cadavers for 3 h per week for 10 weeks. Measured formaldehyde exposures in the breathing zone ranged from 0.49 to 0.93 ppm (geometric mean ± SD = 0.73 ± 1.22). There was a pronounced increase in irritant symptoms over the duration of the each laboratory period, but this effect was stronger at the beginning of the study period. Peak expiratory flow (PEF) declined over the 10 week study by an average of 10 L/min (statistically significant trend in random-effects regression models). Fourteen weeks after ceasing exposures, the group mean baseline PEF had returned to the pre-exposure level. Mean PEF decreased over each laboratory period, although this effect was less noticeable over the course of the semester.

Rhinitis and a wide range of asthma-like conditions can result from exposure to formaldehyde. Some studies have reported that workers exposed to low concentrations may develop severe prolonged asthma attacks after prior exposure; this suggests that they may have become sensitized (Feinman, 1988). However, there is little evidence to suggest that formaldehyde exposure can

result in sensitization through IgE- and IgG-mediated mechanisms (Chang and Gershwin, 1992; Heck *et al*., 1990; Bardana and Montanaro, 1987).

Formaldehyde provocation of human subjects, occupationally exposed to formaldehyde and suffering from asthma-like symptoms such as wheezing, shortness of breath, or rhinitis, occasionally resulted in pulmonary function decrements (2 to 33% response rate) consistent with immediate, delayed, or both immediate and delayed bronchoconstriction (Nordman *et al*., 1985; Burge *et al*., 1985; Henrick and Lane, 1977; Wallenstein *et al*., 1978). While some of the concentrations of formaldehyde that elicited a positive response following provocation tests (6 to 20.7 ppm) were quite high, the authors suggested that formaldehyde-induced bronchial hyperreactivity is due to specific sensitization to the gas. However, no study was able to detect antibodies to formaldehyde which would prove that sensitization to formaldehyde occurs through an immunologic pathway.

In controlled studies with asthmatics from urea-formaldehyde insulated homes, formaldehyde concentrations equal to or greater than those found in indoor environments have not resulted in hematologic or immunologic abnormalities. These tests include: blood count and differential, erythrocyte sedimentation rate; lymphocyte subpopulations (E-rosetting, T3, T4, T8, B73.1, Fc receptor positive lymphocytes and large granular lymphocytes); lymphocyte response to phytohemagglutinin and formalin-treated red blood cells; serum antibody against the Thomsen-Friedenrich RBC antigen and against formalin-RBC; and natural killer, interferon-boosted natural killer, and antibody-dependent cell-mediated cytotoxicity (Pross *et al*., 1987). In addition, nearly all exposure studies on patients with asthma have failed to demonstrate that exposure to formaldehyde results in onset or aggravation of the patients' asthmatic symptoms (Harving *et al*., 1990; Sheppard *et al*., 1984).

The binding of formaldehyde to endogenous proteins creates haptens which can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher *et al.*, 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher *et al.* (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

The effects of formaldehyde on asthmatics appear to be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief durations exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV_1) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m^3) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde

vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

Dermal contact with formaldehyde may result in an erythematous or eczematous dermatitis reaction on exposed areas (Feinman, 1988). Dermal sensitization can result.

Gorski et al (1992) evaluated the production of active oxygen species by neutrophils in 18 persons exposed to 0.5 mg/m^3 formaldehyde for 2 hours. All 13 subjects who had allergic contact dermatitis (tested positive to formaldehyde in skin patch) exhibited significantly higher chemiluminescence of granulocytes isolated from whole blood 30 minutes and 24 hours post-exposure than the individuals who were not formaldehyde sensitive. Thus, the immune cellular response of skin-sensitized individuals to an inhalation exposure to formaldehyde indicates increased production of active oxygen species. The significance of this result is unclear but may have repercussions for toxicological effects mediated by active oxygen species.

Predisposing Conditions for Formaldehyde Toxicity

Medical: Persons with eye, skin, respiratory, or allergic conditions (especially asthma) may be more sensitive to the effects of formaldehyde (Reprotext, 1999). Asthmatics sensitized to formaldehyde may be more sensitive to formaldehyde at low concentrations than non-sensitized individuals.

Chemical: Formaldehyde reacts with hydrochloric acid to form bis-chloroacetyl ether, a carcinogen (Reprotext, 1993).

V. Acute Toxicity to Laboratory Animals

In 72 rats exposed to approximately 600-1,700 mg/m^3 (500-1,400 ppm) formaldehyde vapor for 30 minutes the LC_{50} was found to be 1,000 mg/m^3 (800 ppm) (Skog, 1950). The first deaths did not occur until 6 hours after cessation of exposure. Respiratory difficulty lasted several days after exposure and the last of 49 rats died after 15 days of purulent bronchitis and diffuse bronchopneumonia. Three weeks following exposure, histological examinations of the 23 surviving animals revealed bronchitis, pulmonary microhemorrhages, and edema. No changes were seen in other organs.

A multispecies study by Salem and Cullumbine (1960) showed that a 10-hr exposure to 15.4 ppm (19 mg/m^3) formaldehyde vapor killed 3/5 rabbits, 8/20 guinea pigs, and 17/50 mice. The report stated that formaldehyde exposure resulted in delayed lethality.

Alarie (1981) determined the 10 minute LC_{50} for formaldehyde in mice to be 2,162 ppm (95% confidence interval, 1,687-2,770 ppm). The post-exposure observation period was 3 hours. From the concentration mortality graph provided in the report, an MLE_{05} and BC_{05} of 1,440 ppm and 778 ppm, respectively, could be estimated for a 10 minute formaldehyde exposure. However,

as indicated in the previous reports, delayed deaths occur with formaldehyde which suggests that the 3-hour post-exposure observation period used in this study may not have been long enough.

In other lethality studies, Nagornyi *et al*. (1979) determined a 4 hour formaldehyde LC_{50} in rats and mice to be 588 mg/m³ (474 ppm) and 505 mg/m³ (407 ppm), respectively. However, the raw data for this study were not included in the report. Horton *et al*. (1963) observed that 2 hour exposure of mice to 0.9 mg/l (900 mg/m³) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but 2 hour exposure to 0.14 mg/l (140 mg/m³) did not produce signs of "substantial distress." In a lethality study by Carpenter *et al*. (1946), 250 ppm formaldehyde for 4 hours resulted in deaths of 2-4 out of 6 albino rats (actual number of deaths not specified) and exposure to 125 ppm formaldehyde for 4 hours resulted in deaths of 0-1 out of 6 albino rats.

Swiecechowski *et al*. (1993) exposed groups of five to seven guinea pigs to 0.86, 3.4, 9.4, or 31.1 ppm (1.1, 4.2, 11.6, or 38.6 mg/m³) formaldehyde for 2 hr, or to 0.11, 0.31, 0.59, or 1.05 ppm (0.14, 0.38, 0.73, 1.30 mg/m³) formaldehyde for 8 hours. An 8-hour exposure to $\geq$ 0.3 ppm ($\geq$ 0.4 mg/m³) formaldehyde was sufficient to produce a significant increase in airway reactivity. Similar effects occurred after > 9 ppm (> 11 mg/m³) formaldehyde for the 2-hour exposure group. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine (or carbachol) *ex vivo*. No inflammation or epithelial damage was seen up to 4 days post exposure. The researchers suggest that duration of exposure is important to the induction of airway hyperreactivity and that prolonged (8-hour), low-level exposures may generate abnormal physiologic responses in the airways not detectable after acute (2-hour) exposures.

Male F-344 rats, 7-9 weeks old, were exposed to 0.5, 2, 6 or 15 ppm formaldehyde for 6 hours per day for 1 to 4 days (Monteiro-Riviere and Popp, 1986). Effects noted in the rat nasal respiratory epithelium with 0.5 or 2 ppm were limited to altered cilia with occasional wing-like projections on the ends of the ciliary shafts. Effects noted at 6 ppm for 1 day were autophagic vacuoles in some basal cells, neutrophils in the basal and suprabasal layers, and hypertrophy of goblet and ciliated cells. Loss of microvilli in ciliated cells was noted at all exposure concentrations.

Rats were exposed to 0, 5, 10 or 20 ppm formaldehyde for 3 hours per day on 2 consecutive days (Boja *et al*., 1985). Decreased motor activity and neurochemical changes in dopamine and 5-hydroxytryptamine neurons were reported.

VI. Reproductive or Developmental Toxicity

There are no studies that conclusively show adverse reproductive or developmental effects in animals exposed to formaldehyde (Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988). In humans there are few data on the association of teratogenicity or adverse reproductive effects with formaldehyde exposure. Existing data do not suggest that formaldehyde, by any route, produces significant teratogenic or reproductive effects (Reprotext, Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 94 μg/m³

Study	Kulle *et al*. (1987)
Study population	19 nonasthmatic, nonsmoking human subjects
Exposure method	0.5-3.0 ppm
Critical effects	mild and moderate eye irritation
LOAEL	1 ppm
NOAEL	0.5 ppm
Benchmark concentration	0.44 ppm (BC_{05})
Exposure duration	3 hours
Extrapolated 1 hour concentration	0.76 ppm (0.44^2 ppm* 3 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	not required in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.076 ppm (0.094 mg/m³; 94 μg/m³)

The recommended REL was estimated by a benchmark concentration (BC_{05}) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983). The BC_{05} is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC_{05} from this analysis was 0.44 ppm (0.53 mg/m³) formaldehyde. This value was adjusted to a 1-hour duration using the formula $C^n * T = K$, where n = 2 (AICE, 1989), resulting in a value of 0.74 ppm. An uncertainty factor (UF) of 10 was used to account for individual variation. Generally an uncertainty factor of 3 would be used with the BC_{05} for intraindividual variability, since the BC_{05} accounts for some degree of individual variation. However, information from the literature indicates a wide variability in response to formaldehyde irritancy including reports of irritation (NIOSH HHE reports 1981-1996; Liu et al. 1991; Horvath et al, 1985) or cellular changes associated with irritation and an immune response at levels below the one-hour extrapolated BC_{05} (Pazdrak et al, 1993; Gorski et al, 1992). For these reasons, we used an uncertainty factor of 10 to account for intraindividual variability in the human population.

$$REL = BC_{05}/(UF)$$

The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for response rates of 1% and 5% are compared below. For a graphical representation of the derivation of the REL, refer to section IX.

The study reported by Pazdrak and associates (1993) was not selected as the key study because lack of information on the method used to estimate exposure concentrations and additional limitations in reporting data reduce the level of confidence in this study. The study adds weight,

however, to the REL and to the conclusion that low-level exposures may cause adverse health effects.

Table 1. Comparison of benchmark concentration calculations (1% vs 5%)

Response rate	MLE (ppm)	95% LCL (ppm)
1%	0.50	0.25
5%	0.72	0.44

Level Protective Against Severe Adverse Effects

Based on the results of Green *et al*. (1987), an acute LOAEL of 3 ppm formaldehyde in asthmatics for a duration of 17 minutes (immediately following moderate exercise for 15 minutes) was determined. The researchers felt that, when examined along with the other 3 studies in the series (Kulle *et al*., 1987; Sauder *et al*., 1987; Sauder *et al*., 1986), this study represented a threshold where protective mechanisms of the respiratory tract were beginning to be overwhelmed. Only Green *et al*. (1987) identified 5 out of 39 asthmatic and healthy subjects as having clinically significant decrements in FEV_1 (defined as > 10%). However, 3 of these 5 subjects (out of 39 asthmatic and healthy subjects) responded with a 20% or greater decrease in FEV_1, which is considered a severe adverse effect for acute toxicity exposure. The dose of formaldehyde necessary to produce pulmonary deficits in the Green *et al*. study is consistent with the dose necessary to produce pulmonary deficits in asthmatics or workers in other, less reliable reports (Hendrick *et al*., 1982; Burge *et al*., 1985; Nordman *et al*., 1985).

Because the LOAEL actually represents a threshold for pulmonary effects in asthmatics due to formaldehyde inhalation, and because exercise during exposure was required to observe pulmonary deficits, the LOAEL was considered to be a NOAEL and no uncertainty factor was applied. Note that in Sauder *et al*. (1987) no asthmatic subjects experienced significant bronchoconstriction (> 10% decrease in FEV_1) when exposed to 3 ppm formaldehyde at rest for 3 hours. The 3 ppm value was adjusted to a 1-hour exposure, using a modification of Haber's equation, $C^n \times T = K$, where n = 2 for extrapolation from a shorter duration to 1 hour. The exponent n = 2 was based on findings in the AICE Guidelines (AICE, 1989). The resulting level protective against severe adverse effects is 1.6 ppm for 1-hour exposure to formaldehyde.

Level Protective Against Life-threatening Effects

Alarie (1981) estimated a 10 minute LC_{50} for formaldehyde in mice of 2,162 ppm (95% confidence interval = 1,687-2,770 ppm). The post-exposure observation period was 3 hours. Formaldehyde exposure to 250 ppm (310 mg/m³) for 4 hours killed 4/6 rats within a 14 day observation period (Carpenter *et al., 1*946). Among 72 rats exposed to 600-1,700 mg/m³ formaldehyde vapor for 30 minutes the LC_{50} was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950).

Of the lethality studies summarized above, the study by Alarie (1981) best presents mortality data for the determination of a BC_{05} with an adequate post-exposure period. The major limitation of this study was the short post-exposure observation period of 3 hours. Given the paucity of exposure data resulting in potentially lethal effects, this study currently represents the best estimate for the development of a life-threatening level for formaldehyde. A BED_{05} (which represents an experimental threshold for lethality) of 778 ppm (965 mg/m³) for a 130 minute exposure was estimated from the data (Crump, 1984; Crump and Howe, 1983), but a BC_{05} could not be determined due to lack of data. The BED_{05} was adjusted for a 1-hour exposure using a modification of Haber's equation $C^n \times T = K$, where n = 2 for extrapolation from a shorter duration to a 1 -hour level, resulting in a value of 318 ppm (400 mg/m³). The exponent n = 2 was based on findings in the AICE Guidelines (AICE, 1989). Uncertainty factors applied to the 1-hour BC_{05} were 3-fold to account for interspecies differences and 10-fold for increased susceptibility of sensitive human individuals. The cumulative uncertainty factor was thus 30, which results in an estimated level protective against life-threatening effects of 11 ppm (13 mg/m³) for a 1-hour exposure to formaldehyde.

NIOSH (1995) lists a (revised) IDLH for formaldehyde of 20 ppm based on several reports of acute inhalation toxicity data, mainly in workers. Thus there is no consideration of sensitive subpopulations.

VIII. References

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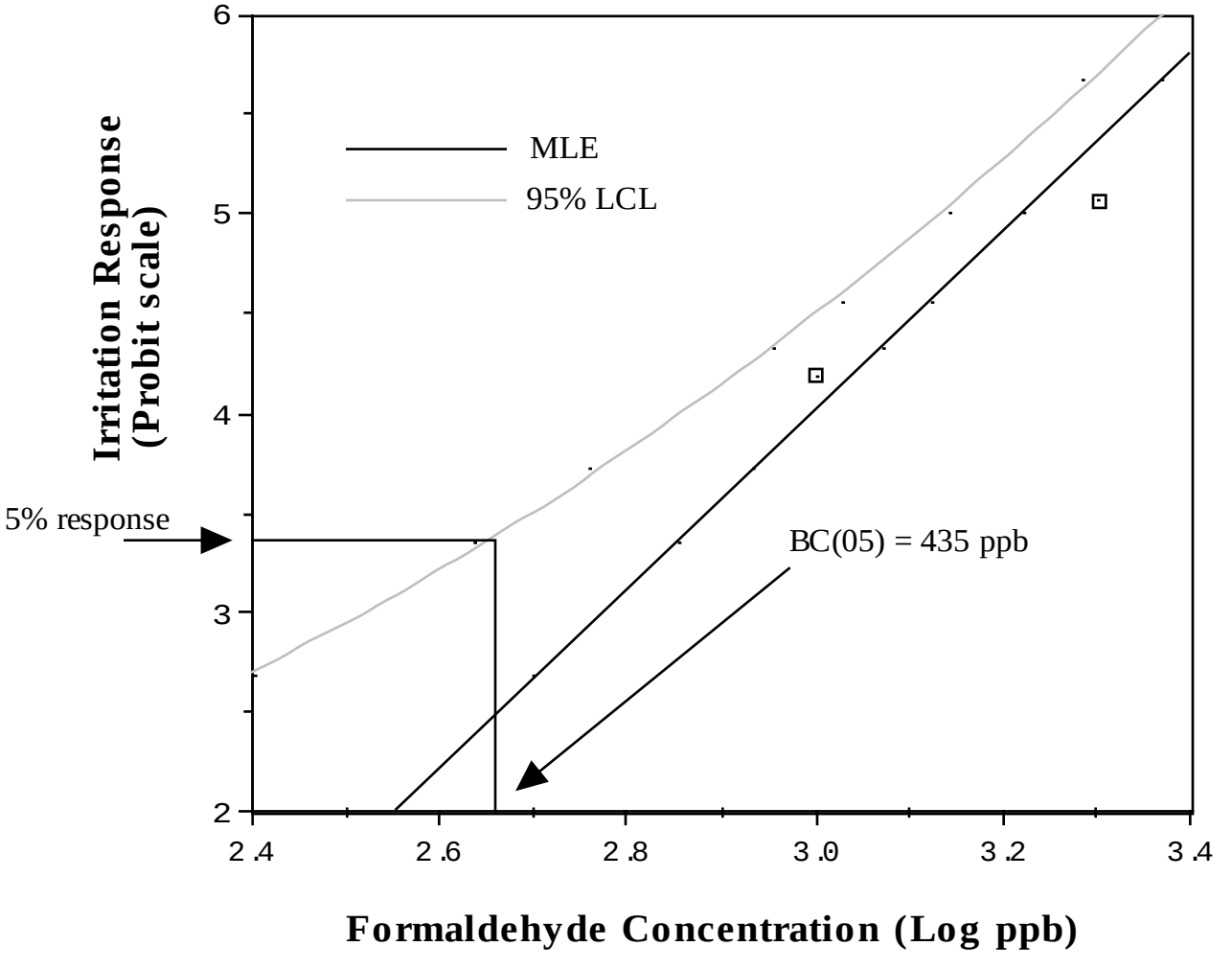
IX. Graphic Representation of Benchmark Concentration Determination


Irritation Response
(Probit scale)
6
5
4
3
2
MLE
95% LCL
5% response
BC(05) = 435 ppb
2.4
2.6
2.8
3.0
3.2
3.4
Formaldehyde Concentration (Log ppb)